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PATENTS

IN THE UNITED STATES PATENT AND TRADMARK OFFICE

Applicants: Jorge D. Brioni, et al.

Serial No.: 09/985,974

Filed: November 7, 2001

Title: THE USE OF SELECTIVE DOPAMINE RECEPTOR AGONISTS FOR TREATING SEXUAL DYSFUNCTION

Group Art No.: 1617

Examiner: Wang, Shengjun

Case No.: 6753.US.02

Date: June 14, 2006

CERTIFICATE OF MAILING (37 CFR 1.8(a)):
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Wanda E. Smith

TRANSMITTAL

MS DAC
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed herewith for the patent application identified above entitled THE USE OF SELECTIVE DOPAMINE RECEPTOR AGONISTS FOR TREATING SEXUAL DYSFUNCTION are the following:

1. Appeal Brief according to 37 C.F.R. § 41.37 (in duplicate)
2. Return Receipt Postcard.

The Commissioner is hereby authorized to charge any additional Filing Fees required under 37 CFR § 1.16, as well as any patent application processing fees under 37 CFR § 1.17 associated with this communication for which full payment had not been tendered, to Deposit Account No. 01-0025. **A duplicate copy of this sheet is enclosed.**

Respectfully submitted,
Jorge D. Brioni, et al.

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AMENDED APPEAL BRIEF ACCORDING TO 37 C.F.R. § 41.37

MS DAC
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is an Amended Appeal Brief in view of the Examiner's final rejection dated October 12, 2005 of Claims 5, 6, 8, 9, 11, 12, 14-23, 25-27 and 29, and after a Notification of Non-Compliant Appeal Brief sent by the Examiner on May 19, 2006. Appellants, by and through their attorney, hereby present their amended brief before the U.S. Patent and Trademark Office Board of Patent Appeals and Interferences in accordance with the provisions of 37 C.F.R. §41.37. Appellants hereby expressly authorize the Commissioner to charge the requisite fees associated with this brief to Deposit Account No. **01-0025**. Triplicate copies of this amended brief are enclosed.

I. REAL PARTY IN INTEREST

Appellants state that the real party in interest of the instant appeal brief is the assignee of record, Abbott Laboratories.

II. RELATED APPEALS AND INTERFERENCES

Appellants state that they know of no other appeals or interferences, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

An Amendment After Final Rejection canceling claims 9, 11, 12, 14-23 and 25 and amending claims 5, 6, 8, 26, 27 and 29 was filed on December 06, 2005. The amendments were entered as per Advisory Action mailed December 29, 2005. Therefore the pending claims are claims 5, 6, 8, 26, 27 and 29. The rejection of rejection of pending claims 5, 6, 8, 26, 27 and 29 is appealed. The appealed claims are set forth in VIII. Appendix.

IV. STATUS OF AMENDMENTS

An Amendment After Final Rejection was filed on December 06, 2005 subsequent to the Examiner's final rejection of October 12, 2005. A Notice of Appeal was also filed on December 06, 2005. According to Advisory Action dated December 29, 2005 the proposed amendments to rejected claims 5, 6, 8, 9, 11, 12, 14-23, 25-27 and 29 were entered but the proposed amendments were not deemed to place the application in condition for allowance.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter of the present invention relates to the use of agonists that are selective to the dopamine receptor subtype D_4 ("D_4 receptor" hereinafter). Preclinical evidence indicates that dopamine ("DA" hereinafter) plays an important role in mediating pro-erectile responses in mammals. The incerto-hypothalamic dopaminergic pathway that innervates the paraventricular nucleus (PVN) and medial preoptic area (MPOA) are associated with the pro-erectile effects of DA (specification page 1, lines 23-30). Clinical data resulting form administration of L-dopa to patients with Parkinson's disease also

indicates the role of DA systems in the CNS on the regulation of sexual male behavior (specification page 2, lines 10-19). Results form *in situ* RNA hybridazation show that expression of the D_4 receptor is high in areas highly related to the facilitation of male sexual behavior (specification page 3, lines 16-28).

Two compounds, N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole have been described as D_4 receptor agonists useful in determining the contribution of D_4 receptors in schizophrenia. However, no specific therapeutic role was assigned to these two compounds (specification page 3, lines 29-33 overlapping to page 4, lines 1-3).

Appellants discovered that the two D_4 receptor agonists, namely N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole, produced a penile erectile response when administered to rats; the response was compared to the response induced by apomorphine, a non-selective D_4 receptor agonist widely used to treat sexual dysfunction (specification pages 13-15, tables 2, 3 and 4). The stimulated sexual response was complemented by an unexpected and therapeutically important finding: the lack of emetic response. Emesis is a side effect that usually accompanies the sexual stimulatory effects of other D_4 receptor agonists, for example apomorphine (specification, pages 16-17, tables 5, 6 and 7). These results, prompted Appellants to recognize that selective D_4 receptor agonists, i.e. compounds that have a higher selectivity for D_4 receptors that for D_2 receptors, especially N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole, are useful to treat sexual dysfunction without the liability of an emetic side effect.

Therefore, Appellants' presently claimed invention encompasses a method of treating sexual dysfunction in a mammal comprising administering a selective D_4 receptor agonists, specifically N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole, or a pharmaceutically acceptable salt thereof (claims 5, 6, and 8). The invention also comprises a method of treating sexual dysfunction in a mammal comprising administering a selective D_4 receptor agonists, specifically N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-

piperazinyl]methyl}-1H-indole, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier (claims 26, 27 and 28).

VI. ISSUES

Whether the Examiner erred in holding that Claims 5, 6, 8, 26, 27 and 29 are unpatentable under 35 U.S.C. §103 over over Fliri *et al.* WO 99/09025 (hereinafter "WO 99/09025") and Glase *et al.* (IDS, hereinafter "Glase") in view of Fliri *et al.* US Patent No. 5,883,094 (hereinafter '094), and Faraci *et al.*, US Patent No. 5,889,010 (hereinafter '010), and in further view of El-Rashidy *et al.*, US Patent No. 5,779,606 (hereinafter '606).

VII. ARGUMENTS

A. The rejection under 35 U.S.C. § 103 of claims 5, 6, 8, 26, 27 and 29 is in error because the combination of references does not present a *prima facie* case of obviousness of the claimed invention.

1. The legal standard under 35 U.S.C. §103.

It is well established law that the PTO has the burden under 35 U.S.C. §103 to establish a case of prima *facie* obviousness (In re Fine, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988)). To satisfy this burden, an Examiner must identify both (i) a suggestion to modify a primary reference in accordance with the teachings of one or more secondary references to achieve the claimed invention and (ii) a reasonable expectation of success in making and using the modified procedure (In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). Furthermore, both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure (In re Dow Chemical Co., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)). The modification must be more than just "obvious to try", which the Court of Appeals for the Federal Circuit has rejected as a standard for obviousness (In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988)). Moreover, in combining references, the Examiner may not use an applicant's disclosure as a guide

or template to select elements or features from among prior art references which, when assembled together, arrive at the claimed invention (In re Fritch, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

2. The Examiner erred in combining the references of WO 99/09025, Glase, US patents '094, '010 and '606 to reject claims 5, 6, 8, 26, 27 and 29 because the references contain no disclosure, which suggests their combination.

Appellants contend that the Examiner erred as a matter of law in combining the five cited references to reject claims 5, 6, 8, 26, 27 and 29, as these references fail to teach or suggest their combination either implicitly or explicitly.

The main reference WO 99/09025 teaches heteroaryl piperazine indole derivatives that bind to D_4 receptors. Appellants' claimed invention is the use of selective D_4 receptor agonists to treat sexual dysfunction. The Examiner correctly noted that the primary reference does not expressly teach the use of the heteroaryl piperazine indole derivatives to treat sexual dysfunction. Additionally, the primary reference does not indicate any biological activity of the claimed compounds, leaving it to understand that these may be agonists, antagonists or have no effect at all after the binding to the receptor. Glase teaches phenyl piperazinyl benzamides that are agonists to the D_4 receptor. The Examiner correctly noted that the Glase does not expressly teach the use of the described compounds to treat sexual dysfunction.

The Examiner however, asserted that this missing information could be found in US patents '094, '010 and '606. An understanding of the prior art references in their entirety, including the pharmacological implications of the teachings, renders this conclusion untenable. US patents '094 and '010 teach benzimidazolone and benzimidazole compounds, respectively, that are able to bind to D_4 receptors. As a whole these references do not teach the actual activity of the compounds claimed, i.e. if the compounds will stimulate or inhibit the DA receptor. It is clearly stated in these references that the claimed compounds "alter" the dopamine mediated neurotransmission, which is not limited to an "increasing or decreasing" of the D_4 dopamine mediated neurotransmission. There is no suggestion or teaching that the compounds claimed in US patents '094 and '010 would even have biological activity. Therefore, even a skilled in

the art would not have been able to determine if the compounds claimed in US patents '094 and '010 would stimulate the sexual responses in a mammal, without pursuing undue experimentation. In addition to the foregoing arguments, Appellants' compounds do not fall into the genus described in US patent '094. US patent '060 teaches a method of treating sexual dysfunction by sublingual administration of apomorphine, which is a non-selective D_4 agonist. Appellants claimed invention specifically refers to the use of D_4 agonists that are not apomorphine, because of the liability of an emetic effect characteristic of apomorphine and other non-selective D_4 agonists. Thus, like for US patents '094 and '010, US patent '606 does no provide a disclosure directed to the subject matter of Appellants' claimed invention

3. The references do not provide a reasonable expectation of success in making and using Appellants' claimed invention.

Appellants contend that the Examiner erred as a matter of law in combining the five named references to reject claims 5, 6, 8, 26, 27 and 29, as these references fail to provide a reasonable expectation of success in making and using Appellants' claimed invention.

WO 99/09025 and Glase to not teach that the disclosed compounds are useful to treat sexual dysfunction. US patents '094 and '010 teach compounds that have D_4 receptor binding activity, without any teaching decribing the agonist or antagonist activity of the disclosed compounds. US patent '060 teaches a method of treating sexual dysfunction using a non-selective D4 agonist, i.e. apomorphine.

The present invention is directed to a method of treating sexual dysfunction using benzimidazoles that act as dopamine agonists selective at the D4 dopamine receptor subtype. Applicants consider of paramount importance that the Examiner recognizes the difference between agonists and antagonists. Definitions are found anywhere, for example, "*Drugs that bind to physiological receptors and mimic the regulatory effects of the endogenous signaling compounds are termed* ***agonists****. Other drugs bind to receptors without regulatory effect, but their binding blocks the binding of the endogenous agonist. Such compounds, which may still produce useful effects by inhibiting the action of an agonist (e.g., by competition for agonist binding sites), are termed* ***antagonists****.*" Chapter 2. Pharmacodynamics: Mechanisms of drug action and the relationship between drug

concentration and effect, *Elliott M. Ross, Terry P. Kenakin* (Goodman & Gilman's The Pharmacologic Basis of Therapeutics - 10th Ed. (2001))

Also, "***Agonist*** *drugs bind to and activate the receptor in some fashion, which directly or indirectly brings about the effect... .. Pharmacologic* ***antagonist*** *drugs, by binding to a receptor,* ***prevent*** *binding by other molecules".* Basic Principles 1. Introduction - *Bertram G. Katzung, MD, PhD* (Basic and Clinical Pharmacology - 9th Ed. (2004)). Also, according to the Merriam Webster Medical Dictionary an **antagonist** is *"a chemical that acts within the body to reduce the physiological activity of another chemical substance (as an opiate); especially: one that opposes the action on the nervous system of a drug or a substance occurring naturally in the body by combining with and blocking its nervous receptor".* An **agonist** is *"a chemical substance (as a drug) capable of combining with a receptor on a cell and initiating the same reaction or activity typically produced by the binding of an endogenous substance".* Therefore, even for a skilled in the art, it would be very difficult to predict and have a reasonable expectation of success in making selective D4 agonists to treat sexual dysfunction from the disclosures of the references cited. It is impermissible hindsight for the Examiner, in combining references, to use an applicant's disclosure as a guide or template to select elements or features from among prior art references which, when assembled together, do not even arrive at the claimed invention (In re Fritch, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

B. The unexpected results achieved by Appellants' claimed invention rebut any *prima facie* obviousness rejection.

Even if the Examiner has established a *prima facie* case of obviousness, Appellants contend that it has presented evidence of secondary considerations to rebut and overcome the obviousness rejection (Graham v. John Deere Co., 86 S.Ct. 684, 694 (1966)). Appellants have shown that the claimed compounds of the invention stimulate the sexual behavior in rats in a similar way as apomorphine (specification pages 14 and 15, Tables 3 and 4). Appellants also have shown that the claimed compounds of the invention do not induce emesis at any dose (specification pages 16-17, Tables 6 and 7) as apomorphine does. Accordingly, the data reported in Tables 3, 4, 6 and 7 of Appellants' specification establish evidence of unexpected results, which support the assertion that

the claimed compounds are agonist selective for only the D_4 receptor and therefore useful to treat sexual dysfunction with the advantage of lacking the emetic unwanted side effect.

C. Conclusions

The cited references, either alone or in combination, do not teach or suggest a method of treating sexual dysfunction using the selective agonists of the D4 dopamine receptor claimed in the invention. Furthermore, the combined teachings of the references do not provide one of ordinary skill in the art with a reasonable expectation of success in using the compounds of the present invention for treating sexual dysfunction. Thus, the Examiner failed to establish a *prima facie* case of obviousness of Appellants' claimed invention. Alternatively, Appellants' showing of unexpected results rebuts any finding of obviousness.

VIII. CLAIM APPENDIX

1-4. (Cancelled)

5. (Currently Amended) A method of treating sexual dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a selective dopamine D_4 receptor agonist wherein said selective dopamine D_4 receptor agonist is selected from the group consisting of N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole or a pharmaceutically acceptable salt thereof.

6. (Currently Amended) A method of treating male sexual dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a selective dopamine D_4 receptor agonist wherein said selective dopamine D_4 receptor agonist is selected from the group consisting of N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole or a pharmaceutically acceptable salt thereof.

7. (Cancelled)

8. (Currently Amended) A method of treating male erectile dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a selective dopamine D_4 receptor agonist wherein said

selective dopamine D_4 receptor agonist is selected from the group consisting of N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole or a pharmaceutically acceptable salt thereof.

9. (Cancelled) The method of claim 6 wherein said selective dopamine D_4 receptor agonist is N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide or a pharmaceutically acceptable salt thereof.

10. (Cancelled)

11. (Cancelled) The method of claim 8 wherein said selective dopamine D_4 receptor agonist is N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide or a pharmaceutically acceptable salt thereof.

12(Cancelled) The method of claim 6 wherein said selective dopamine D_4 receptor agonist is 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole or a pharmaceutically acceptable salt thereof.

13. (Cancelled)

14(Cancelled) The method of claim 8 wherein said selective dopamine D_4 receptor agonist is 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole or a pharmaceutically acceptable salt thereof.

15. (Cancelled) The method of claim 5 wherein said selective dopamine D_4 receptor agonist is 25 fold more selective for the D_4 receptor than for the D_2 receptor.

16(Cancelled) The method of claim 5 wherein said selective dopamine D_4 receptor agonist is 50 fold more selective for the D_4 receptor than for the D_2 receptor.

17. (Cancelled) The method of claim 5 wherein said selective dopamine D_4 receptor agonist is 100 fold more selective for the D_4 receptor than for the D_2 receptor.

18(Cancelled) The method of claim 5 wherein said selective dopamine D_4 receptor agonist is 200 fold more selective for the D_4 receptor than for the D_2 receptor.

19(Cancelled) The method of claim 5 wherein said selective dopamine D_4 receptor agonist is 300 fold more selective for the D_4 receptor than for the D_2 receptor.

20. (Cancelled) The method of claim 5 wherein said selective dopamine D_4 receptor agonist is 500 fold more selective for the D_4 receptor than for the D_2 receptor.

21. (Cancelled) The method of claim 5 wherein said selective dopamine D_4 receptor agonist is 1000 fold more selective for the D_4 receptor than for the D_2 receptor.

~~22.~~ (Cancelled) ~~A method of treating sexual dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a selective dopamine D_4 receptor agonist or a pharmaceutically acceptable salt thereof wherein said agonist does not cause significant emesis.~~

~~23~~(Cancelled) ~~A method of treating male sexual dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a selective dopamine D_4 receptor agonist or a pharmaceutically acceptable salt thereof thereof wherein said agonist does not cause significant emesis.~~

24. (Cancelled)

~~25~~(Cancelled) ~~A method of treating male erectile dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a selective dopamine D_4 receptor agonist or a pharmaceutically acceptable salt thereof thereof wherein said agonist does not cause significant emesis.~~

26. (Currently Amended) A method of treating sexual dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a selective dopamine D_4 receptor agonist wherein said selective dopamine D_4 receptor agonist is selected from the group consisting of N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

27. (Currently Amended) A method of treating male sexual dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a selective dopamine D_4 receptor agonist wherein said selective dopamine D_4 receptor agonist is selected from the group consisting of N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

28. (Cancelled)

29. (Currently Amended) A method of treating male erectile dysfunction in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a selective dopamine D_4 receptor agonist wherein said selective dopamine D_4 receptor agonist is selected from the group consisting of N-{[4-(2-cyanophenyl)-1-piperazinyl]methyl}-3-methylbenzamide and 5-fluoro-2-{[4-(2-pyridinyl)-1-piperazinyl]methyl}-1H-indole or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

30. (Cancelled)

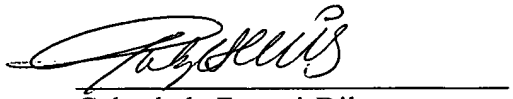
IX. EVIDENCE APPENDIX

There is no evidence to append.

X. RELATED PROCEEDING APPENDIX

There are no related proceedings to append.

Respectfully submitted,
Jorge D. Brioni, et al.



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